Table I. Comparative Titrations of Organomagnesium and Organolithium Reagents

organometallic reagent	solvent	titer, N method A[a]	method B[b]	method C[c]
n-C_4H_9Li[d]	hexanes	2.55	2.49	2.62
t-C_4H_9Li[e]	hexanes	2.16	2.13	2.10
CH_3MgCl	THF	2.50[f]	2.50	2.93
CH_3MgBr	Et_2O	2.90[f]	2.97[g]	3.08
$C_8H_{17}MgBr$	Et_2O	1.70[f]	1.71	1.83
sec-C_4H_9MgBr	Et_2O	0.88	0.80	1.42
sec-C_4H_9MgBr	Et_2O	0.81	0.80	0.89
C_6H_5MgBr	Et_2O	3.30[f]	3.20	3.76
$(sec$-$C_4H_9)_2Mg$	Et_2O	0.72[f]	0.70	1.05

[a] 1,10-Phenanthroline was used as an indicator (ref 2). [b] N-Phenyl-1-naphthylamine was used as an indicator (see text). [c] Total base determined by titration of an aqueous quench of an aliquot of the organometallic reagent to a phenophthalein end point using 0.1 N HCl. The variance between values for this titration and those of method A or B is due to other basic impurities. [d] Double titration of this organolithium reagent using dibromoethane (ref 3) showed this organolithium reagent to be 2.50 N. [e] Double titration of this organolithium reagent using dibromoethane (ref 3) showed this organolithium reagent to be 2.07 N. [f] Poorly defined end point had to be estimated. In some cases, addition of THF helped to clarify the end point of these 1,10-phenanthroline titrations. [g] Average of five titrations ranging from 2.91-3.07 M.

end points. Old solutions of vinylmagnesium bromide which produce colored solutions after a protic quench obscure the end point of this and other colorimetric procedures.

In our procedure, the relatively acidic N-phenyl-1-naphthylamine was used in either of two ways. First, a small amount of the diarylamine was added to a stock solution (0.05 M in N-phenyl-1-naphthylamine) of xylene containing a known concentration of *sec*-butyl alcohol (0.25 M). This alcohol–xylene indicator solution was then added to the organometallic reagent of interest in either an ethereal or hydrocarbon solvent until the yellow-orange color disappeared. Alternatively, a small amount (ca. 50 mg) of the diarylamide was added directly to a flask to which the organometallic reagent was then added. Subsequent titration with a 0.29 M xylene solution of *sec*-butyl alcohol until the yellow-orange color of the indicator had disappeared then determined the titer of the organometallic reagent.

Examples of the results obtained with this titration procedure are shown in Table I along with a comparison to other commonly used analytical procedures used to determine the concentration of typical organolithium and organomagnesium reagents. These data show the procedure we have developed is both general and reliable. The titers determined by our procedure vary by less than ±3%, apparently due to volumetric errors occurring during transfer of small volumes of organometallic reagent by syringe.[7]

Although there is no advantage to using this procedure in titrations of very common organolithium reagents like n-butyllithium, this procedure seems to be more useful in cases where alkylmagnesium halides are titrated. In such cases, the diarylamide procedure we describe consistently gives reliable end points while the best alternative method (the 1,10-phenanthroline procedure) gives end points of varying quality depending on the nature of the alkyl group attached to magnesium in the organomagnesium reagent.

(7) The reproducibility of measuring volumes by syringe, ±2% with calibrated syringes (ref 8, p 207), limits reproducibility of this technique as well as those described in ref 1–6 which also typically employ syringes to transfer solutions.

Experimental Section

Hydrocarbon and ethereal solvents were distilled from sodium/benzophenone prior to use. Organolithium and organomagnesium reagents were purchased from Aldrich Chemical Co. or prepared by using unexceptional procedures. The indicating acid, N-phenyl-1-naphthylamine, was purchased from Aldrich and purified prior to use by recrystallization from alcohol. Purified N-phenyl-1-naphthylamine can be kept for at least 1 year without significant discoloration in nitrogen-flushed bottles. Xylene solutions (0.005 M) turned yellow-brown during the same period, plausibly because of adventitious oxidation. Standard techniques for handling air-sensitive organometallic reagents were used throughout this work.[8]

Analysis of Methylmagnesium Bromide. To a flame-dried, 50-mL round-bottomed flask under nitrogen containing a magnetic stirring bar was added 2 mL of an ether solution of methylmagnesium bromide. This flask was then connected to a buret containing a xylene solution of N-phenyl-1-naphthylamine (0.005 M) and *sec*-butyl alcohol (0.25 M) by means of a hypodermic needle connected to a Luer fitting on the buret. While the flask was vented to a mineral oil bubbler, the titrant was added dropwise to a stirred solution. A yellow-orange color[9] which initially formed continued to deepen until at last enough *sec*-butyl alcohol had been added to react with all the amide and Grignard reagent. At this point the deep yellow-orange color disappeared and a cloudy white suspension formed. If more ether solvent was present initially the colored solution changed to give a water white solution. A modification of this procedure which avoids the necessity of storing xylene solutions of N-phenyl-1-naphthylamine has also proven successful. In this modified procedure, ca. 50 mg of N-phenyl-1-naphthylamine was first added to the flame-dried flask. Addition of a Grignard reagent then produced N-phenyl-1-naphthylamide which was titrated with 0.29 M *sec*-butyl alcohol in xylene as described above.

Acknowledgment. Support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

Registry No. N-Phenyl-1-naphthylamine, 90-30-2; CH_3MgBr, 506-83-2; n-C_4H_9Li, 109-72-8; t-C_4H_9Li, 594-19-4; CH_3MgCl, 676-58-4; $C_8H_{17}MgBr$, 17049-49-9; sec-C_4H_9MgBr, 922-66-7; C_6H_5MgBr, 100-58-3; $(sec$-$C_4H_9)_2Mg$, 17589-14-9.

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(9) Lithium N-phenyl-1-naphthylamide has a λ_{max} at 440 nm while bromomagnesium N-phenyl-1-naphthylamide has a λ_{max} at 401 nm.

Synthesis of *cis*- and *trans*-7,8-Dihydrodiols of 7-Methylbenzo[*a*]pyrene

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Received July 15, 1980

We recently reported that a methyl substituent in a polycyclic aromatic hydrocarbon (PAH) does not necessarily block the enzymatic formation of a dihydrodiol at the methyl-substituted aromatic double bond.[1] This enzymatic reaction is now known to occur in vitro for many methylated PAH's in rat liver microsomal enzyme sys-

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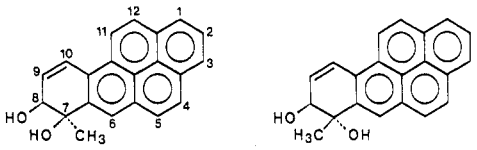
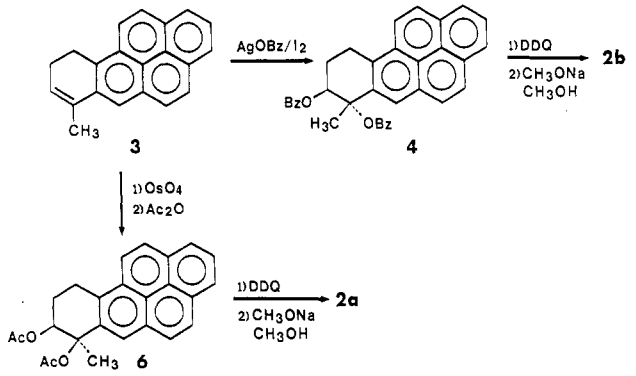
tems.[2] Because of the difficulty in obtaining sufficient amounts for detailed characterization, the stereochemistry of dihydrodiol metabolites formed at the methyl-substituted carbons cannot be unequivocally established. We now report the synthesis of *cis*- and *trans*-7,8-dihydrodiols (**2a** and **2b**) of 7-methylbenzo[*a*]pyrene (**1**). Due to the availability of the title compounds, the *trans* isomer **2b** has been identified as a metabolite of **1** in rat liver microsome incubations.[3]



2a **2b**

The preparation of **2a** and **2b** began with 9,10-dihydro-1 (**3**) which was synthesized according to a known procedure.[4] Conversion of **3** into **2b** was accomplished by carrying out the Prévost reaction using silver benzoate and iodine, followed by dehydrogenation with DDQ in benzene under refluxing conditions, and then methanolysis as employed previously.[5-7] Reaction of **3** with OsO_4 in pyridine and acetylation of the reaction product gave *cis*-7,8-diacetoxy-7,8,9,10-tetrahydro-1 (**6**) which upon dehydrogenation with DDQ and methanolysis afforded **2a** in good yield.[7]



The cis configuration of **2a** was confirmed by its ability to form an acetonide upon reaction with anhydrous acetone in the presence of anhydrous $CuSO_4$;[8] **2b** did not form any acetonide under identical conditions. There exist two possible conformations for both cis isomer **2a** and trans isomer **2b**, respectively. However, the ^1H NMR coupling constants of the cis isomer **2a** ($J_{8,9}$ = 5.9, $J_{8,10}$ < 0.5 Hz) indicate C_8-OH is preferentially in the quasi-axial conformation whereas both hydroxyl groups of the trans isomer **2b** ($J_{8,9}$ = 2.2, $J_{8,10}$ = 3.0 Hz) are preferentially in a quasi-equatorial conformation.[9,10] Since previous NMR spectral analysis indicated that both *cis*- and *trans*-7,8-dihydrodiols of benzo[*a*]pyrene have the preferred conformations[7,9] similar to those of **2a** and **2b**, respectively, it is apparent that the methyl substituent at the hydroxylated carbon does not alter the preferred dihydrodiol conformation. This report thus confirms the validity of acetonide formation in the determination of the cis/trans configurations and the use of NMR coupling constants for the conformational assignment of the methyl-substituted dihydrodiols.[1]

High-performance liquid chromatographic analysis of the rat liver microsomal incubation product of **2b** indicated the formation of *trans*-7,8-diol 9,10-epoxide.[3] This supports the hypothesis that **2b** may be the proximate carcinogenic metabolite of **1**, as suggested earlier by Newman.[11]

Experimental Section[12]

9,10-Dihydro-7-methylbenzo[*a*]pyrene (3). This compound was prepared according to a published procedure[4] in a 70% yield: mp 155–156 °C (benzene–hexane) (lit.[4] mp 155–156 °C); NMR (acetone-d_6) δ 2.34 (s, 3, CH_3), 2.48 (m, 2, H_9), 3.49 (t, 2, H_{10}), 6.17 (apparent t, 1, H_8), 8.0–8.4 (m, 8, aromatic).

***trans*-7,8-Bis(benzoyloxy)-7,8,9,10-tetrahydro-1 (4).** A solution of **3** (1.26 g, 5 mmol) in benzene (60 mL) was added to the solution of silver benzoate (15 mmol) and I_2 (7.5 mmol) in benzene (150 mL) which had been previously refluxed for 30 min. The resulting solution was heated at reflux for 48 h under N_2. The precipitate was removed by filtration through Celite. The filtrate was partitioned between ethyl ether and dilute aqueous sodium hydroxide. The organic layer was separated, washed with water, and dried ($MgSO_4$), and solvent was removed. The crude product was chromatographed on a Florisol column; **4** was eluted with benzene and the eluant was evaporated to dryness to yield colorless solid (1.78 g, 70%): mp 200–201 °C; mass spectrum, *m/e* 510 (M^+); NMR ($CDCl_3$) δ 2.09 (s, 3, CH_3), 2.53–2.61 and 2.72–2.78 (m, 2, H_9), 3.60–3.80 (m, 2, H_{10}), 6.64 (dd, 1, $J_{8,9}$ = 4.4 Hz, $J_{8,9'}$ = 11.8 Hz, H_8), 7.27–8.21 (m, 18, aromatic).

***trans*-7,8-Bis(benzoyloxy)-7,8-dihydro-1 (5).** A solution of **4** (510 mg, 1 mmol) and DDQ (340 mg, 1.5 mmol) in benzene (100 mL) was refluxed under N_2 for 20 h. Chromatography on neutral alumina column eluted with benzene gave **5** (380 mg, 75%): mp 296–297 °C (benzene–hexane); mass spectrum, *m/e* 508, (M^+); NMR ($CDCl_3$) δ 1.56 (s, 3, CH_3), 6.29 (dd, 1, H_9), 7.31 (t, 1, H_8), 7.42–7.58 (m, 6, aromatic), 7.62 (dd, 1, H_{10}), 7.91–8.18 (m, 11, aromatic), 8.38 (d, 1, H_{11}) ($J_{8,9}$ = $J_{8,10}$ = 2.2, $J_{9,10}$ = 10.3 Hz).

***trans*-7,8-Dihydroxy-7,8-dihydro-1 (2b).** A solution of **5** (254 mg, 0.5 mmol) in THF (15 mL) and $NaOCH_3$ (60 mg, 1.1 mmol) in methanol (12 mL) was stirred at 65 °C for 20 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was collected, washed with water, and dried over $MgSO_4$. After solvent was removed, **2b** was obtained as a light yellow solid (123 mg, 82%): mp 192–193.5 °C dec; mass spectrum, *m/e* 300 (M^+) NMR (acetone-d_6) δ 1.51 (s, 3, CH_3), 4.86 (apparent s, 1, H_8), 6.27 (dd, 1, H_9), 7.52 (dd, 1, H_{10}), 7.98–8.32 (m, 6, $H_{1-5,12}$), 8.46 (d, 1, H_{11}), 8.58 (s, 1, H_6) ($J_{8,9}$ = 2.2, $J_{9,10}$ = 10.3, $J_{8,10}$ = 3.0, $J_{11,12}$ = 8.8 Hz).

***cis*-7,8-Diacetoxy-7,8,9,10-tetrahydro-1 (6).** A solution of **3** (3 g, 11.2 mmol) and OsO_4 (3 g, 11.9 mmol) in pyridine (50 mL) was stirred at ambient temperature for 3 weeks. Sodium bisulfite (10 g) in water (100 mL) was added, and the solution was stirred for 4 h. The precipitate was filtered, washed with water, and dried under vacuum overnight. The crude product was acetylated by stirring with pyridine (30 mL) in acetic anhydride (300 mL) at room temperature overnight. Addition of water gave crude **6** which was purified via chromatography on a Florisil column eluted with benzene. Crystallization from benzene gave pure **6** as light yellow prisms (3.01 g, 72%): mp 167–168 °C; mass spectrum, *m/e* 386 (M^+) NMR ($CDCl_3$) δ 1.73 (s, 3, CH_3), 2.02 (s, 6, OAc), 2.2–2.31

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(12) Melting points are uncorrected. ^1H NMR spectra were measured on a Bruker WH 270-MHz spectrometer with Me_4Si as internal standard. All new compounds gave satisfactory microanalysis for C and H and/or mass spectra consistent with the structural assignments.

and 2.52–2.60 (m, 2, H_9), 3.44–3.50 (m, 3, H_{10}), 5.27–5.29 (dd, 1, $J_{8,9}$ = 2.2, $J_{8,9'}$ = 5.9 Hz, H_8), 7.93–8.20 (m, 7, $H_{1-5,11,12}$), 8.51(s, 1, H_6).

***cis*-7,8-Diacetoxy-7,8-dihydro-1 (7).** Reaction of **6** with DDQ under the same conditions (except at 55 °C) as described for **5** gave **7** in 93% yield: mp 252–253 °C; mass spectrum, *m/e* 384 (M^+); NMR ($CDCl_3$) δ 1.65 (s, 3, CH_3), 1.98 (s, 3, OAc), 2.06 (s, 3, OAc), 5.22 (d, 1 H_8), 6.52 (dd, 1, H_{10}), 7.72 (d, 1, H_{10}), 8.00–8.21 (m, 6, aromatic), 8.38 (d, 1, H_{11}), 8.56 (s, 1, H_6) ($J_{8,9}$ = 5.2, $J_{9,10}$ = 10.3, $J_{10,11}$ = 9.56 Hz).

***cis*-7,8-Dihydroxy-7,8-dihydro-1 (2a).** Methanolysis of **7** with $NaOCH_3$ under conditions as described for **2b** gave **2a** in 78% yield: mp 240–242 °C; mass spectrum, *m/e* 300 (M^+); NMR (acetone-d_6) δ 1.52 (s, 3, CH_3), 4.08 (d, 1, H_8), 6.52 (dd, 1, H_9), 7.72 (d, 1, H_{10}), 8.00–8.61 (m, 8, aromatic) ($J_{8,9}$ = 5.9, $J_{9,10}$ = 9.6, $J_{8,10}$ < 0.5 Hz).

Synthesis of Acetonide of 2a. This compound was synthesized according to the published procedure[8] in 95% yield; mass spectrum, *m/e* 249, 254, 282, 283, 340 (M^+). The UV absorption characteristics are closely similar to those of **2a**.

Acknowledgment. We thank Dr. D. W. Miller for obtaining the ^1H NMR spectra, and Mr. J. Clark and Mrs. A. Y. Haung for technical assistance.

Registry No. 2a, 75625-90-0; **2b**, 75625-91-1; **3**, 7499-32-3; **4**, 75625-92-2; **5**, 75625-93-3; **6**, 75625-94-4; **7**, 75625-95-5; silver benzoate, 532-31-0.

A New Synthesis of Cyclodecane- and Cycloundecane-1,3-dione

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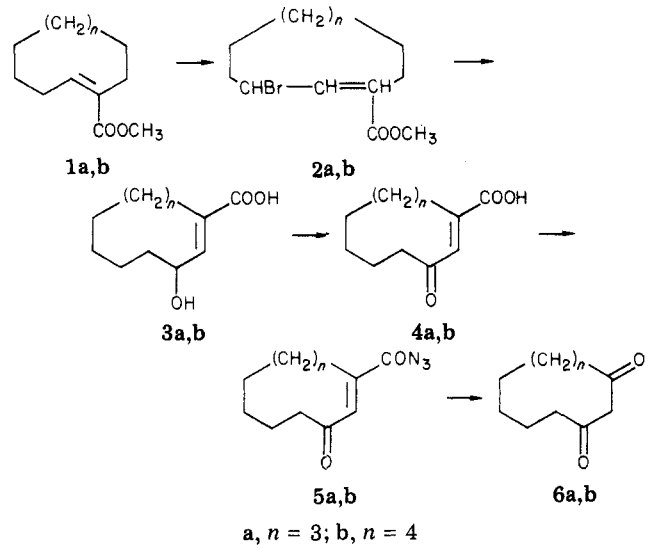
Received April 28, 1980

Continuing our work on the photochemical behavior of the isoxazolophanes,[1] we found it necessary to find an entry to cyclodecane- and cycloundecane-1,3-dione. The method should be simpler than the one reported in the literature[2] which used cyclododecanone and cycloundecanone, respectively, as the starting materials. We now report a new synthesis (Scheme I) of the title compounds starting from (methoxycarbonyl)cyclodec-1-ene (**1a**) and its homologue **1b**.[3] Allylic bromination with NBS of the starting materials afforded in both cases only the 3-bromo derivatives (**2a,b**). Although the reaction is stereospecific, we have not elements to assign univocally the stereochemistry of **2a,b**.

From **2a,b** the corresponding hydroxy acids (**3a,b**) were obtained by reaction with KOH–H_2O–Me_2SO, in 48–50% yield, purifiable as the insoluble K salt. Jones oxidation of **3a,b**, gave the 3-oxo acids (**4a,b**) which were converted into the acyl azides (**5a,b**) via the mixed anhydride method.[4] Thermal decomposition of the acyl azides **5a,b** followed by acidic treatment of the intermediate isocyanate afforded the 1,3-diones (**6a,b**).

Scheme I



a, n = 3; b, n = 4

The advantages of this synthesis are (i) availability of our starting materials which served only as intermediates for the preparation of starting materials (cyclodecanone and cycloundecanone) in the reported synthesis,[2] (ii) a fewer number of chemical steps with good overall yields, via stable and purifiable intermediates.

The stereochemistry of the double bonds, as reported in Scheme I, was assigned on the basis of the following data: (i) the methyl esters of **3b** and **4b** were identical with known compounds;[5] (ii) the chemical shifts of the vinyl protons of compounds **3a–5a** are in agreement with those of cycloundecene derivatives **3b–5b**; (iii) the chemical shift of the vinyl proton of the methyl ester of **4a** is at δ 7.29; short-time irradiation of this methyl ester allows to show the presence of its isomerization product which is intermediate in the photochemical deconjugation reaction leading to a mixture of the known[6] (*E*)- and (*Z*)-3-(methoxycarbonyl)cyclodec-3-enones; the chemical shift of vinyl proton of the above unisolable intermediate ester is at higher field (δ 6.46), inferred from the reaction mixture, than that of the methyl ester of **4a**, supporting the *E* configuration of the latter in agreement with a literature report.[7] $NaBH_4$ reduction of the methyl ester of **4a** affords the same hydroxy ester obtained from **3a** with CH_2N_2.

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian EM-390 instrument; chemical shifts are reported in parts per million from internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 377 spectrophotomer. UV spectra were taken on a Varian Cary 219 (EtOH solutions).

1-(Methoxycarbonyl)-3-bromocycloalk-1-ene (2a,b). A mixture of (methoxycarbonyl)cycloalk-1-ene (**1a,b**; 0.2 mol), azobis(isobutyronitrile) (0.5 g), and NBS (0.21 mol) in CCl_4 (300 mL) was heated under reflux, with stirring, for 2 h. [**Caution**: The reaction may start very exothermically.] After cooling, the reaction mixture was filtered, and the filtrate was washed with water (2 × 50 mL) and dried. The residue from the solvent evaporation afforded the bromo ester (**2a,b**). **2a**: 46 g, 83.6%, as undistillable oil; NMR ($CDCl_3$) 6.9 (1 H, d, J = 11 Hz), 5.3 (1 H, m), 3.8 (3 H, s), 2.55 (2 H, m), 2.3 (2 H, m), 1.4 (10 H, m); IR (film) 1710, 1630 cm^{-1}. **2b**: 29.6 g; 51.3%; mp 64 °C.[5]

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